QT interval analysis in type 2 diabetic patients

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Summary:-

Background: The electrocardiographic QT interval has been extensively studied in diabetes mellitus. Recently, there has been increasing interest in the relationship between diabetes and QT abnormalities .The QT interval, which is easily obtained from a standard resting electrocardiogram(ECG), reflected the total duration of ventricular myocardial depolarization and repolarization. The heart rate corrected QT interval (QTc) by Bazett's formula on the electrocardiogram has been proposed as a risk factor for ventricular arrhythmias in diabetes mellitus. Dispersion of QT(QTd) is defined as the difference between maximum and minimum QT interval QT interval on 12 lead ECG, which reflected spatial ventricular repolarization in homogeneity ,has been report to increase in diabetic subjects compare with non diabetic subjects.

Patients and Methods: Type 2 diabetic patients (n=80) and healthy subjects (n=25) were required to have 12-lead ECG suitable for QT analysis ,QT interval was measured in each lead to found(maximum, minimum, and mean).QT interval vary according to the heart rate, it can be corrected using Bazett's formula to give QTc interval, and to found (maximum, minimum, and mean).Dispersion of QT interval(QTd) was calculate using the difference between the maximum and minimum QT interval duration as same as for dispersion of corrected QT interval(QTcd).

Result: There were significant difference in QT interval indices between type 2 diabetic and healthy subjects ($P<0.05$) as well as the correct QT interval indices. ROC curve analysis of QT and QTc interval duration parameters demonstrated that no QT parameters performs better than maximum and minimum of QT and QTc, areas under ROC curve were(0.69 and 0.66 $P<0.001$)for maximum and mean QT respectively and (0.80 and 0.75 $P<0.001$) for maximum and mean QTc respectively. From this result we can say that QTc parameters better than QT parameters in context of patients and control differences. In multiple linear regression models, maximum, mean, and dispersion of QT interval were significantly affect by diabetes mellitus after adjustment for age, gender, body mass index (BMI), and heart rate. Whereas, only maximum and mean QTc were significantly affected by diabetes mellitus after adjustment for age, gender, and BMI. Prolongation of QT interval (QTc and QTd) also seen in a diabetic subjects which significant different as compare to the healthy subjects.

Conclusion: The result of this study indicate that corrected QT interval (maximum and mean)in a routine ECG is a useful marker to identify the QT abnormalities differentiating diabetes type 2 from healthy subjects.

Key words: ECG – QT interval – Diabetes mellitus**.**

Fac Med Baghdad 2010; Vol. 52, No.4
Received Mar, 2010
Accepted June. 2010

Introduction:

The QT interval in the electrocardiogram (ECG) reflects the total duration of ventricular myocardial depolarization and repolarization .It has been shown that a prolonged QT interval is associated with sudden death and poor survival in healthy subjects [1], and in a variety of clinical conditions including newly diagnosed type 2 diabetes [2], and type 1 diabetes [3] [4]. The observation that the QT interval exhibits a certain degree of spatial variability on the epicardial surface [5] has led to the hypothesis that differences in the duration of the QT interval between ECG leads may reflect heterogeneity in recovery of excitability [6] . Based on the evidence that non uniform repolarization provides a substrate for the development of malignant ventricular arrhythmias [7].The interlead differences in the QT interval duration and the range of the duration , termed "QT dispersion "(QTd), was proposed as on index of the spatial dispersion of the ventricular recovery times [8] . It was proposed that the different ECG leads magnify the ECG signal of different myocardial region and that, consequently, QT dispersion is almost a direct measure of the heterogeneity of myocardial repolarization[8].

Many studies have shown clinical and prognostic importance of increased QT interval and QT dispersion in various non cardiac diseases, these are type 1 and type 2 diabetes mellitus DM [9]. There has been considerable interest in the relationship between diabetes and QT interval prolongations which has been postulated to be involved in the increased mortality of diabetic patients [10].

Accordingly, the present study was planned to estimate QT indices in patients with type 2 diabetes and healthy subjects. As well as evaluation the prolongation of the corrected QT interval and prolongation of QT dispersion in type 2 diabetic patients.

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Method:

Study population: Randomly eighty diabetic patients with type 2 diabetes enrolled from the national diabetes center in AL-mustansiriyi University (2008-2009). Mean age of diabetic patients was 55±10.1 years (51 male and 29 female) with body mass index (BMI) of 29±4.2 Kg/ m^2,which calculated according to the following equation:

BMI = weight (Kg)/ [height (m)]^2 [11] .

Twenty five healthy subjects were studied, their mean age was 32±7.4 year (13 male and 12 female), and their BMI was 25±2.9 Kg/m^2.These patients with diabetes history taking anti-diabetic medicine.

QT wave analysis in 12-Lead ECG:

12-lead surface electrocardiogram (ECG) was performed for all subjects involved in this study. RR and QT interval were measured manually with a ruler on the resting ECG tracing [[12][13][14], three consecutive beats were considered on the 12-lead ECG to measure QT interval duration and QT dispersion [15]. The QT interval was measured from the beginning of the QRS complex to the end of the down slope of the T wave (crossing of the isoelectric line) [16].Surface resting 12-lead ECG was obtained at a paper speed of 25 mm/sec, standardized at mv/cm. (cardio smart, version 1.4, 22743582 GA (e), Germany).

Since the QT interval on its own may vary according to the heart rate, it was corrected using Bazett's formula [17], [QTc =QT/$(RR)^{1/2}$] to give QTc intervals .The QTc value for each subject was considered as the mean value of the two calculated intervals in one lead , then calculated the mean QTc in 12-lead ECG .

The following indices were derived from ECG Leads

1. The maximum of QT (ms) or corrected QT $(ms)^{1/2}$ interval duration in any measurable leads, among 12-Lead ECG (QT maximum, QTc maximum).
2. The minimum of QT (ms) or corrected QT $(ms)^{1/2}$ interval duration in any measurable leads, among 12-Lead ECG (QT minimum, QTc minimum).
3. The mean of QT (ms) or corrected QT $(ms)^{1/2}$ interval duration of all measurable ECG leads (QT mean, QTc mean).
4. QT interval dispersion (QTd) as a difference between the maximum and minimum QT interval duration.
5. Corrected QT interval dispersion (QTcd) as a difference between the maximum and minimum of corrected QT interval duration.

QTc more than 440$ms^{1/2}$ (0.44$s^{1/2}$) and QTd over 80ms (>0.080s) were considered abnormally prolonged [18][19].

Statistical analysis: Differences in QT and corrected QTc indices of patients and control were assessed using t-test; results are shown as mean ± standard error (SE). The standard error is a measure of variability for the obtained estimate of mean (sample mean), P value less than (0.05) was statistically significant. Receiver Operator Characteristic (ROC) analysis was used to assess the validity parameters of a test with values measured on a continuously scale. Receiver Operator Characteristic (ROC) analysis is a widely accepted method for analysis and comparing the diagnostic accuracy for selecting the best QT wave index in differentiating between patients and control.

In ROC curve, the area under curve give an idea about the usefulness of the test and helps in comparing it to other test, the closer area to one (ideal test) the most validities. Multiple linear regression analysis was used to assess of QT interval indices in patients compare to control. The patients and control difference in frequencies was assessed by (chi-square).

Result:

Result were based on QT interval duration analysis in a sample of (80) diabetic patients and a comparable group of (25) control subject.

The mean value of selected QT interval duration parameters (maximum, minimum and mean) were significantly higher among cases with diabetes mellitus (DM) compare to control, table (1). The variability indices of QT interval dispersion show a small a mount of changes when compared to mean QT interval.

The same pattern of difference was also observed in corrected QT interval duration indices, table (2).

ROC analysis was used to assess the usefulness of different QT and QTc parameters in differentiating diabetic from control. As shown in table (3) among QT parameters the maximum and mean QT interval duration had the most important role. The same conclusion applies to QTc interval duration parameters. When comparing the role of the maximum and mean QT and QTc parameters; it was evident that QTc parameters performed better than QT parameters in the context of patients and control differences as shown by a large ROC area. The multiple linear regression model was use to study the net effect of diabetes compared to control on selected QT indices after adjusting for age, gender, BMI, in addition to heart rate membership, table (4), only the maximum, mean ,and dispersion of QT parameters were significantly affected by diabetes disease. All these models were statistically different and able to explain an amount ranging between (0.199 to 0.588) of variation in the dependent variable. Where as in table(5) only the maximum and mean of corrected QT interval were significant affected by diabetes disease, these model were statistically different ranging between (0.398 to 0.42) of variation in the dependent variable. As shown in table (6) 32.5% of diabetic patients have QT interval corrected for heart rate (QTc) more than 440$(ms)^{1/2}$ were considered abnormally prolonged which significantly different (P<0.05) compare with control which have (QTc) less than 440$(ms)^{1/2}$. While, 17.5% of diabetic patient were QTd more than 80ms which considered abnormally prolonged

and significantly different from control which have (QTd) less than 80ms. It was found that QTc was more sensitive criteria than QTd to compare diabetes with control.

Table 1: The patients and control difference in mean of selected QT interval duration indices

	Normal subjects (n=25)	**Diabetic subjects (n=80)**	**P value**
1.Minimum QT interval duration (ms)			
Range	(300 - 380)	(260 - 440)	0.039
Mean±SE	333 ± 4.3	345 ±3.6	
2.Maximum QT interval duration (ms)			
Range	(330 - 420)	(340 - 570)	0.001
Mean±SE	382 ± 5.3	407 ±4.3	
3.Mean QT interval duration (ms)			
Range	(321 - 402)	(309 - 480)	0.004
Mean±SE	361 ±4.8	379 ±3.5	
4.QT interval dispersion (ms)			0.003
Range	(30 - 80)	(20 - 160)	
Mean±SE	49 ± 3.1	62 ± 3.1	

ms :- millisecond

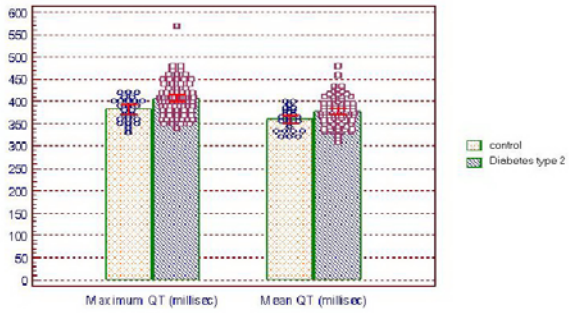

Figure 1: QT interval (maximum and mean) in patients and control

Table 2: The patients and control difference in mean of selected corrected QT interval duration indices

	Normal subjects (n=25)	Diabetic subjects (n=80)	P value
1.Minimum QTc $(ms)^{1/2}$			0.049
Range	(289 - 431)	(300 - 451)	
Mean±SE	356 ± 6.8	372 ±3.9	
2.Maximum QTc $(ms)^{1/2}$			<0.001
Range	(318 - 476)	(404 - 554)	
Mean±SE	426 ± 7.1	465 ±3.5	
3.Mean QTc $(ms)^{1/2}$			<0.001
Range	(310 - 448)	(375 - 508)	
Mean±SE	398 ± 6.4	428 ±2.9	
4.QTc dispersion $(ms)^{1/2}$			0.002
Range	(29 - 118)	(11 - 183)	
Mean±SE	70 ± 5.9	94 ± 4.6	

ms :- millisecond

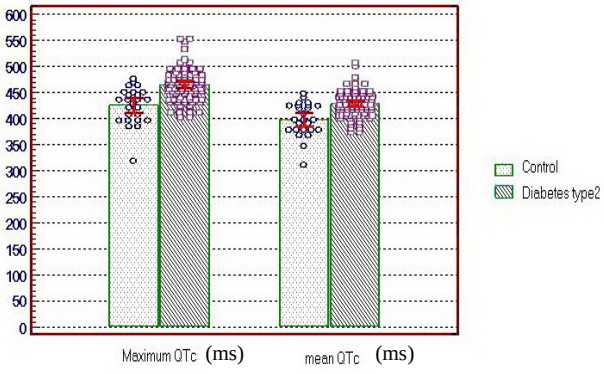

Figure 2: QT interval (maximum and mean) in patients and control

Table 3: ROC area under the curve of selected QT and corrected QT(QTc) interval indices in the context of differentiating diabetics from normal subjects

	QT interval duration		**Corrected QT interval duration (QTc)**	
	ROC area	**P Value**	**ROC area**	**P value**
1. Minimum(ms)	0.628	0.06[NS]	0.63	0.05[NS]
2. Maximum(ms)	0.693	0.004	0.804	<0.001
3. Mean(ms)	0.667	0.012	0.757	<0.001
4. Dispersion (ms)	0.643	0.031	0.671	0.01

P<0.05(significant) NS: not significant

Table 4: Multiple linear regression models showing the regression coefficient for being a diabetic (compared to normal subjects) adjusted for age, gender, BMI and heart rate using selected QT interval indices as response (dependent) variable

	Partial regression coefficient	**P value**	**R^2 model**	**P value**
1.Minimum QT interval duration (ms)	2	0.84[NS]	0.429	<0.001
2.Maximum QT interval duration (ms)	22.4	0.05	0.569	<0.001
3.Mean QT interval duration (ms)	15.1	0.09	0.588	<0.001
4.QT interval dispersion (ms)	20.3	0.05	0.199	0.014

P<0.05(significant) NS: not significant

Table 5: Multiple linear regression models showing the regression coefficient for being a diabetic (compared to normal subjects) adjusted for age, gender and BMI using selected corrected QT interval indices as response (dependent) variable

	Partial regression coefficient	P value	R^2 model	P Value
1. Minimum QTc $(ms)^{1/2}$	10.7	0.46[NS]	0.186	0.01
2. Maximum QTc $(ms)^{1/2}$	28.2	0.032	0.42	<0.001
3. Mean QTc $(ms)^{1/2}$	20.3	0.06	0.398	<0.001
4. QTc dispersion $(ms)^{1/2}$	17.5	0.29[NS]	0.104	0.13[NS]

P<0.05(significant) NS: not significant

Table 6: The patients and control difference in relative frequency of prolonged corrected QT and prolonged QT interval dispersion

	Total	Prolonged QTc [>440($ms)^{1/2}$]		Prolonged QT interval dispersion (>80 ms)	
Study group	N	N	%	N	%
Control	25	1	4	0	0
diabetes	80	26	32.5	14	17.5
P (Chi-square)		0.004		0.025	

N: number

Discussion:

Patients with diabetes mellitus (DM) are at an increased risk of dying from cardiovascular disease [20], the reason for which is not completely understood, excess cardiovascular risk in this population persists even after normalization for the other conventional cardiovascular risk factors (hypertension, dyslipidaemia, physical inactivity, smoking) suggesting that there are other incompletely mechanisms which increase cardiovascular risk in diabetic patients. Ventricular instability, as manifested in QT abnormalities, might be an important additional mechanism [21]. In addition, several studies in type 1 diabetes [19] and type 2 diabetes [9] [13] found that QT abnormalities were not influenced by duration of diabetes. Veglio etal study[9] show the clinical and prognostic importance of increased QT interval and QT dispersion in type 1 and type 2 diabetes mellitus(DM).Therefore this study designed to compare the effect of type2 diabetes on the QT and correct QT interval indices as compare with control.

In this study, data of type 2 diabetes show a significant differences of QT interval duration indices (maximum, minimum, and mean) in comparison with control, these findings agree with previous study [22]. QT dispersion(QTd) reflect spatial difference in myocardial recovery time[8],healthy subjects exhibit a small degree of QTd[23], while increased in people with type 1 and type 2 diabetes as compare to non diabetic subjects [9] . Our results were in consistent with finding of other studies [19] [24] where the QTd in type 2 diabetes vs control was (62±3.1 ms vs 49±3.1 ms).

Increased QTd may indicate non-uniform ventricular repolarization, thus possibly providing a substrate for the development of malignant ventricular arrhythmias. Endocardial monophasic action potential studies have demonstrated that there are regional differences in the duration of myocardial repolarization that may be reflected in the surface ECG [25]. The result of this study found that whole corrected QT interval duration indices were highly significant in type 2 diabetes as compare with control, this is in accordance with previously studies on diabetic patients type 2 [26] [9] [20].

The areas under the ROC curve for maximum and mean QT intervals were (0.693 and 0.667 respectively). Also for maximum and mean QTc intervals were (0.804 and 0.757 respectively), these four indices were the most important measurements in discriminating between type 2 diabetes and normal subject. From ROC analysis it was found that QTc maximum was more sensitive index which refer to QT interval abnormalities in diabetic patients type 2, these agree with previous study [27] [6] which indicated that, the diabetes is a known to be associated with impaired parasympathetic cardiac control, this is reflected in a reduced ability to regulate heart rate therefore increased QTc interval value. In fact it was found that QTd and QTcd in type 2 diabetes significantly different as compare with normal subjects but the best indices were (maximum and mean QT) and (maximum and mean QTc).

In the present study, diabetic subjects were significantly different in a body mass index(BMI),and heart rate which previously reported by Dan[28],this problem was adjusted for control by multiple regression model, which a adjusted for age, gender, BMI, and heart rate, after this adjustment found that maximum, mean, and dispersion of QT contributed significantly in this model to explain the affected by diabetes disease ,whereas after adjustment for age, gender, and BMI only the maximum and mean QTc which standing the effect of being diabetic. Among eighty type 2 diabetic subject in our study were (26) patients with QTc over (440 $ms^{1/2}$) and (14) patients with QTd over (80 ms), which significantly different as compare with control, QTc more sensitive prolongation than QTd when compare between patients and control.These values of QTc and QTd were considered abnormally prolonged in type 2 diabetes according to previous study [18][19] [24].

Disturbed glucose metabolism of the heart may have directly contributed to an impaired myocardial electrical stability. Interestingly in a report of previous study, QTc duration was associated with level of insulin and glucose tolerance [29].The authors speculated that reduce myocardial glucose uptake may be involved in impaired cardiac

repolarization as indicated by a prolongation of QT interval. QT prolongation may also result from cardiac adrenergic dysinervation with altered balance of sympathetic and parasympathetic cardiac neuroactivity[30][31][32] and/or myocardial cell defects[33]and lead to a reduced electrical stability in diabetic patient [34].

In conclusion, the present study has shown that the QT interval parameters give additional prognostic information in patients with type 2 diabetes mellitus and measurements of the QTc interval indices (mean and maximum) may be favored in this context given that it is simple to do and may represent a stronger prognostic marker than other QT indices.

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